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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Dent disease (Dent-1 and Dent-2)

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DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Dent-1 disease.

X-linked recessive hypophosphatemic rickets, X-linked recessive nephrolithiasis, low-molecular-weight proteinuria with hypercalciuric nephrocalcinosis, Dent's Japan disease, Japanese Dent('s) disease, idiopathic low-molecular-weight proteinuria of Japanese children.

There is genetic heterogeneity: see also Dent-2 disease, which is caused by mutations in the *OCRL* gene.

1.2 OMIM# of the disease

Dent disease-1 (MIM #300009).

X-linked recessive hypophosphatemic rickets (MIM #300554).

X-linked recessive nephrolithiasis with renal failure (MIM #310468).

Low-molecular-weight proteinuria with hypercalciuric nephrocalcinosis (MIM #308990).

Dent-2 disease (MIM #300555).

1.3 Name of the analyzed genes or DNA/chromosome segments

CLCN5, Xp11.22-p11.23.

OCRL, Xq25-q26.1.

1.4 OMIM# of the gene(s)

CLCN5, 300008.

OCRL, 300535.

1.5. Mutational spectrum

More than 200 Dent-1 disease patients with *CLCN5* defects have been described, with disease-causing mutations scattered throughout the gene.[1–6] The mutational spectrum includes missense (44%) and nonsense (26%) mutations, small deletions/insertions (15%) and splice defects (11%), with a few hotspots, mainly affecting arginine codons. Large insertions/deletions may be detected in around 4% of the patients.[6]

OCRL mutations in Dent-2 disease patients are not uniformly distributed. Missense mutations are mainly found in exons 8–15, nonsense or frameshift mutations almost always affect exons 1-7.[6,7]

Human wild-type ClC-5/OCRL-1 with their corresponding exon numbering are deposited in GenBank, accession nos. NG_007159.2 and NP_000267.2. *CLCN5* and *OCRL* mutations are included in the Human Gene Mutation Database (http://www.hgmd.org/) or can be obtained via the Leiden Open Variation Database (http://grenada.lumc.nl/LOVD2/MR/home.php?select_db=CLCN5 or http://www.ncbi.nlm.nih.gov/lovd/home.php?select_db=OCRL). Novel data should be shared through these databases.

1.6 Analytical methods

Bi-directional Sanger sequencing of PCR-amplified products comprising the total coding region and the exon-intron boundaries of the *CLCN5* gene and, when negative, the *OCRL* gene.

1.7 Analytical validation

Confirmation of the detected mutation at least from a second amplicon, preferentially from an independent biological sample of the index case. Pathogenicity of novel missense variants has to be verified by (i) testing a set of at least 100 chromosomes from normal ethnically matched controls, (ii) considering its deposition in single-nucleotide polymorphism databases and (iii) using *in silico* prediction methods. The gold standard is analysis of functional consequences of the respective *CLCN5*/*OCRL* mutation in *Xenopus laevis* oocytes or cell models, performed in a few laboratories in the world. Gene transcripts should be analyzed in case of splice mutations.

1.8 Estimated frequency of the disease (Incidence at birth ('birth prevalence') or population prevalence)

To date, around 250 families with Dent-1 disease and about 50 patients with Dent-2 disease have been reported. Based on these data and considering the highly variable presentation, disease frequency cannot be estimated.

1.9 If applicable, prevalence in the ethnic group of investigated person

Not applicable.

1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☒	☐
C. Risk assessment in relatives	☒	☐
D. Prenatal	☒	☐

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Comment:

The clinical presentation of Dent disease is frequently subtle with the majority of patients being asymptomatic in childhood. Many patients are identified through urine screening for hematuria and proteinuria, a current method in Japanese school children.[1,8]

Although nephrocalcinosis and hypercalciuria are characteristic findings in Dent disease, only low-molecular-weight proteinuria is uniformly present in all patients.[9,10]

Additional features observed in patients are aminoaciduria (in 40-50%), phosphate (in 20-25%) and potassium wasting (in 5-15%), glycosuria (in 10-20%), renal tubular acidosis (in 3-5%) and renal failure in adulthood.[9] Manifestations of Dent disease are highly variable, even within the same family, and there is no genotype-phenotype correlation.[10]

Dent-2 disease is caused by mutations in *OCRL*, the gene previously identified as the cause of the oculo-cerebro-renal syndrome (Lowe syndrome, OMIM 309000).[11,12] Patients show a renal phenotype comparable to Dent-1 disease, except for a lower prevalence of nephrocalcinosis.[9] Dent-2 disease may present with additional (mild) extra-renal features of the Lowe syndrome spectrum, for example, peripheral cataracts, mild cognitive and/or mental impairment, stunted growth and elevated serum CK/LDH levels.[9]

Prenatal diagnosis is feasible if the familial mutation is known but is of no clinical benefit.

2. TEST CHARACTERISTICS

2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)
Close to 100%. The sensitivity of sequence analysis of PCR-amplified products approaches 100%. A lot of variants have been tested functionally,[13–16] and the pathogenicity of most mutants has been predicted by publically available algorithms. Nonetheless, errors may occur due to allele dropout and mutations outside the coding region in the promoter, polyA-site, enhancers or intronic variants may be missed.

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
Nearly 100%. In rare cases, variants may erroneously be interpreted as pathogenic.

2.3. Clinical sensitivity
(proportion of positive tests if the disease is present)
Mutations in *CLCN5* (Dent-1 disease; 60%) and *OCRL* (Dent-2 disease; 15%) account for 75% of cases with a phenotype of Dent disease. Sensitivity around 75%.

2.4 Clinical specificity
(proportion of negative tests if the disease is not present)
The clinical specificity can be dependent on variable factors, such as age or family history. In such cases, a general statement should be given, even if a quantification can only be made case by case.

Close to 100%.

2.5 Positive clinical predictive value
(life-time risk to develop the disease if test is positive)
100%. But considerable variability in symptoms.

2.6 Negative clinical predictive value
(probability of not developing the disease if the test is negative)
Mutation demonstrated in index case from the family: 100%.

Index case in that family not been tested: Consider the X-linked recessive mode of inheritance. If *CLCN5* and *OCRL* are both normal, the negative predictive value is 75%.

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: The person is clinically affected
3.1.1 Can a diagnosis be made other than through a genetic test?

No		
Yes	Clinically	☒
	Imaging (ultrasound)	☒
	Endoscopy	☐
	Biochemistry	☒
	Electrophysiology	☐
	Other: No tracer uptake on DMSA scan (non-specific)	

Abbreviation: DMSA, dimercaptosuccinic acid.

3.1.2. Describe the burden of alternative diagnostic methods to the patient
The diagnosis of Dent disease is based on a high index of clinical suspicion, as the presenting symptoms are non-specific (proteinuria, kidney stones, renal failure).

The biochemical diagnosis of Dent disease is not invasive (spot urine for low-molecular-weight proteinuria, hypercalciuria and variable presence of other proximal tubular dysfunctions). Nephrocalcinosis and kidney stones can usually be demonstrated by abdominal ultrasound. The amount of total protein excretion may be in the nephrotic range, suggesting a glomerular disease. In this situation, genetic testing can avoid a renal biopsy, which is an invasive and potentially dangerous (bleeding) procedure.

Genetic testing may be crucial in patients presenting with end-stage renal disease, as the urine tests are unreliable in this setting (decrease in calcium excretion, non-specific low-molecular-weight proteinuria from tubulo-interstitial damage).

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
The cost effectiveness of renal ultrasound and biochemical studies is very high.

As low-molecular-weight proteinuria is an obligate finding in Dent disease, this test is of crucial importance and can replace genetic testing in siblings of a genetically proven index case. In this situation, urine biochemistry is much more cost-effective than genetic testing. The presence of other biochemical findings in Dent disease is variable.

3.1.4 Will disease management be influenced by the result of a genetic test?
Yes. In cases with nephrotic range proteinuria, who might undergo a renal biopsy or receive immunosuppressive therapy.[17]

3.2 Predictive Setting: the tested person is clinically unaffected but carries an increased risk based on family history.
3.2.1 Will the result of a genetic test influence lifestyle and prevention?
If genetics test demonstrates the presence of mutated allele, high fluid intake is indicated to prevent renal stone formation, and nephrological follow-up will be initiated. Supplementation of electrolytes or alkali if needed. Potential additional medical interventions, such as

pharmacological therapy of hypercalciuria and potassium citrate (see 4). Monitoring of kidney function.

3.2.2. Which options in view of lifestyle and prevention does a person at risk have if no genetic test has been done?
Urine could be tested for the presence of low-molecular-weight proteinuria, which is an obligate finding in Dent disease.

3.3 Genetic risk assessment in family members of a diseased person
3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
Yes, if a mutation is demonstrated.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes. If the index case has known mutations, siblings, parents and other family members can be screened for disease by testing urine for low-molecular-weight proteinuria.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Yes.

3.4 Prenatal diagnosis
3.4.1 Does a positive genetic rest result in the index patient enable a prenatal diagnosis?
Yes.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for a patient or his/her relatives?

Follow-up is warranted in patients with Dent disease. Potential medical interventions include high fluid intake, thiazide diuretics[18] and potassium citrate supplementation.[19] Animal studies suggest a positive effect of citrate suppletion in a *Clcn5* knockout mouse model (on kidney function and calcium deposits).[19] Human data have documented a decrease in hypercalciuria with thiazide diuretics,[18] yet at the expense of hypokalemia in some patients. The long-term efficacy on the progression of renal failure has not been studied, however.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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